CANCER PREVENTION

Prospects for a Prophylactic Vaccine Against Papilloma Viruses

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Abstract

Cervical cancer is a leading cause of cancer among women. Over 450,000 new cases of this disease are diagnosed each year and one-third of these cases perish due to the disease. Research over the past several decades has proven that human papillomaviruses (HPV) are closely linked to the development of cervical cancer and its precursors, known as SIL (squamous intraepithelial lesions). In fact, data suggest that over 90% of cervical cancer cases worldwide are linked to HPV and that four HPV types (16, 18, 31, 45) account for over three-fourths of these cases. This understanding has led many to propose that a vaccine against HPV might be an effective means of reducing cervical cancer incidence worldwide. In support of this, studies in dogs, rabbits, and cows have clearly shown that vaccination with a virus-like particle (VLP) that consists of the self-assembled structural protein of the papillomavirus protects against subsequent viral challenge. Furthermore, this protection has been shown to be mediated by neutralizing antibodies. Based on these promising initial findings, human trials of HPV vaccines have been initiated. These initial trials and plans for an NCI-sponsored 20,000 woman randomized trial to evaluate the efficacy of a VLP-based HPV vaccine will be discussed.

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Summary of Talk

Human papillomaviruses (HPVs) are associated with the development of numerous tumors, most notably cervical cancer. With respect to cervical cancer, HPV is known to be causally linked to all stages of cervical carcinogenesis, including the mostly benign low-grade squamous intraepithelial lesions of the cervix (LSIL), the more advanced high-grade SIL (HSIL) and invasive cervical cancer. In fact, over 90% of all cervical cancer cases diagnosed worldwide are associated with HPV infections (1; 2). Studies that have examined the association between HPV infection and cervical cancer have observed that women infected with one of the over 30 types of HPV that infect the cervix are 15-50 times more likely than uninfected women to develop cervical cancer (2-5). Even more strikingly, those infected with cancer associated HPV types (including HPV 16 and 18) are over 100 times more likely than those who are uninfected to develop cervical cancer. Given this strong link between HPV and cervical cancer, it is believed that prevention of cervical cancer is possible via vaccination against HPV. Two broad classes of HPV vaccines are currently under development: prophylactic and therapeutic vaccines (6; 7). Prophylactic vaccines are designed to prevent initial infection and the establishment of LSIL. These vaccines are designed to induce antibodies against HPV that are capable of neutralizing the virus and thereby prevent infection. Most of the prophylactic vaccines under evaluation are based on the structural proteins of HPV, known as the L1 and L2 proteins. The most promising prophylactic vaccine to date is the virus-like particle vaccine (VLP vaccine).

In contrast to the prophylactic vaccines, therapeutic vaccines are designed to be able to eradicate an HPV infection or established HPV-related cervical lesion after infection has occurred. These vaccines are designed to induce a cell-mediated (rather than antibody) response capable of recognizing and fighting HPV infected cells. Various therapeutic vaccines are currently under investigation but the majority are based on HPV proteins important for the maintenance of infection (E2) or for transformation (E6/E7).

There is increasing evidence from animal studies that the VLP-based vaccines are effective prophylactic vaccines. Three animal models currently exist where vaccination with VLPs has successfully prevented infection: the bovine, canine, and rabbit models (8-10). In each of these models,

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vaccination with VLP-based vaccines has induced high levels of neutralizing antibodies against the virus and these antibodies have been shown to prevent infection or the development of lesions in nearly all vaccinated animals. The fact that the protection afforded by vaccination with VLPs is mediated by antibodies was nicely demonstrated in a canine study where transfer of sera from vaccinated dogs to unvaccinated dogs protected the unvaccinated dogs against subsequent viral challenge.

Based on these animal studies, safety and immunogenicity trials have been initiated in humans. In one such study sponsored by NCI, 72 men or women volunteers were enrolled into one of seven vaccination or placebo arms. Participants received three doses of HPV VLP vaccine (or placebo) and were followed for reactogenicity and immunogenicity for a period of five months. Ten and 50ugs of VLP were evaluated in this initial Phase I trial, with and without the adjuvants Alum and MF59. All but five participants tested negative for HPV16 antibodies at entry. After vaccination, antibody titers observed among vaccinated individuals were much higher than those observed among the placebo group, and among the vaccination groups those vaccinated with 50ug of VLP without adjuvant had the highest overall titers. Titers observed using 50ug of VLP with MF59 were comparable to those observed using 50ug of VLP with no adjuvant and those observed with 50ug of VLP plus Alum were lower. Thus there is no evidence that adjuvant augmented antibody production. Importantly, the side effects associated with vaccination have been minimal. While mild local pain lasting less than a day at the site of infection was reported with some frequency (57%), other side effects at the site of inoculation, such as erythema and induration, were rare; no such symptoms were reported after more than 7% of vaccinations. The only systemic symptoms reported with some frequency were transient headaches, which were reported after 11% of the vaccinations. Other systemic symptoms reported were also transient and included nausea (after 2.2% of vaccinations), malaise (1.6%), and myalgia (1.1%). Based on these promising findings, a larger trial of 200 women was initiated to evaluate further reactogenicity and immunogenicity of the 50ug VLP vaccine administered without adjuvant. This Phase II trial is schedule to be completed by the end of April 2000. To date over 130 women have volunteered for this phase II trial and results (still masked) suggest that reactogenicity is similar to what was observed in the initial study of 72 individuals.

In addition to the VLP-only trials, additional trials are planned over the coming year to evaluate the safety and immunogenicity of a chimeric VLP vaccine containing the E2 and E7 proteins, in addition to L1. This chimeric vaccine, if effective, would have both a prophylactic effect (via antibodies generated against the L1 protein) and a therapeutic effect (via cell mediated responses generated against the E2 and E7 proteins).

Pending successful completion of the Phase I and II trials, NCI is planning a larger, 20,000 woman Phase III trial to evaluate the effectiveness of the vaccines shown to be safe and immunogenic in Phase I and II studies.

References

1. Bosch, F.X., Manos, M.M., Munoz, N., Sherman, M.E., Jansen, A., Peto, J., Schiffman, M.H., Moreno, V., Shah, K.V., and the IBSCC study group Prevalence of HPV DNA in cervical cancer in 22 countries. J Natl Cancer Inst, 87(11): 796-802, 1995.
2. Herrero, R., Hildesheim, A., Bratti, C., Sherman, M.E., Hutchinson, M., Morales, J., Balmaceda, I., Greenberg, M.D., Alfaro, M., Burk, R.D., Wacholder, S., and Schiffman, M. A population-based Study of Human Papillomavirus Infection and All Grades of Cervical Neoplasia in Rural Costa Rica. JNCI, 1998.
3. Eluf-Neto, J., Booth, M., Munoz, N., Bosch, F.X., Meijer, C.J., and Walboomers, J.M. Human papillomavirus and invasive cervical cancer in Brazil. British Journal of Cancer, 69: 114-119, 1994.
4. Munoz, N., Bosch, F.X., deSanjose, S., Tafur, L., izarzugaza, I., Gili, M., Viladiu, P., Navarro, C., Martos, C., Ascunce, N., Gonzalez, L.C., Kaldor, J.M., Guerrero, E., Lorincz, A., Santamaria, M., deRuiz, P.A., Aristizabal, N., and Shah, K. The causal link between human papillomavirus and invasive cervical cancer: A population-based case-control study in Columbia and Spain. Int J Cancer, 52: 743-749, 1992.
5. Peng, H., Liu, S., Mann, V., Rohan, T., and Rawls, W. Human papillomavirus types 16 and 33, Herpes simplex virus type 2 and other risk factors for cervical cancer in Sishuan province, China. Int.J.Cancer, 47: 711-716, 1991.
6. Schiller, J.T. and Lowy, D.R. Papillomavirus-like particles and HPV vaccine development. Current Concepts Immunol, 1997.(in press)
7. McNeil, C. HPV vaccine treatments proliferate, diversify (News). JNCI, 89: 280-281, 1997.
8. Breitburd, F., Kirnbaure, R., Hubbert, N.L., Nonnenmacher, B., Trin-Dinh-Desmarquet, C., Orth, G., and Schiller, J.T. Immunization with viruslike particles from cottontail rabbit papillomavirus (CRPV) can protect against experimental CRPV infection. J Virol, 69(6): 3959-3963, 1995.
9. Kirnbauer, R., Chandrachud, L.M., O'Neil, B.W., Wagner, E.R., Grindlay, G.J., Armstrong, A., McGarvie, G.M., Schiller, J.T., Lowy, D.R., and Campo, M.S. Virus-like particles of Bovine Papillomavirus type 4 in prophylactic and therapeutic immunization. Virology, 219: 37-44, 1996.
10. Suzich, J.A., Ghim, S.J., Palmer-Hill, F.J., White, W.I., Tamura, J.K., Bell, J.A., Newsome, J.A., Jenson, A.B., and Schlegel, R. Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas. Proc.Natl.Acad.Sci, 92: 11553-11557, 1995.